SOLID PHASE TRANSFORMATION OF CARBAMAZEPINE-FUMARIC ACID CO-CRYSTAL

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ABSTRACT

The study is about the solid phase transformation of carbamazepine-fumaric acid co-crystal. Pharmaceutical area is the most importance part in human live. In pharmaceutical, the solubility of the active pharmaceutical ingredients (API) is importance physical property to be studied. Co-crystal formation is an example method to improve the solubility of an API. Carbamazepine is an API which has low solubility. In this study carbamazepine and fumaric acid are used to form co-crystal in ethanol as a solvent. The objective of this research is to study the solid phase transformation of carbamazepine-fumaric acid co-crystal. Initially the solubility of the carbamazepine is measured using gravimetric and High Performance Liquid Chromatography (HPLC). Later, the co-crystal transformation study will be proceed via varying the ratio of fumaric acid to carbamazepine using slurry method. Carbamazepine and fumaric acid are characterized using Thermal Gravimetric Analysis (TGA) and Fourier Transform Infrared Spectroscopy (FTIR). The result shows the solubility of carbamazepine and fumaric acid increased as temperature increased. The Fourier Transform Infrared Spectroscopy (FTIR) spectrums show the main spectrum frequency (absorption region in cm^{-1}) for carbamazepine and fumaric acid. Thermo Gravimetric Analysis **(**TGA) analysis showed the total decomposition for carbamazepine is approximately at 250 °C and for the fumaric acid at 260 °C. As the conclusion the solubility of carbamazepine and fumaric acid has been increased as the temperature increased. Due to the time constraints and the technical failure of the equipment (High Performance Liquid Chromatography (HPLC)) during the analysis has resulted the co-crystal transformation study could not be completed.

ABSTRAK

Kajian ini adalah mengenai transformasi fasa pepejal asid carbamazepine-fumaric bersama kristal. Bidang farmaseutikal adalah bahagian yang paling penting dalam kehidupan manusia. Dalam farmaseutikal, kelarutan bahan aktif farmaseutikal (API) adalah aspek fizikal yang penting untuk dikaji. Pembentukan kristal adalah contoh satu kaedah untuk meningkatkan kebolehlarutan API. Carbamazepine adalah API yang mempunyai kelarutan yang rendah. Dalam kajian ini carbamazepine dan asid fumaric digunakan untuk membentuk bersama-kristal dalam etanol sebagai pelarut. Objektif kajian ini adalah untuk mengkaji transformasi fasa pepejal carbamazepine- asid fumaric bersama kristal. Pada mulanya keterlarutan daripada carbamazepine diukur menggunakan gravimetrik dan Kromatografi Cecair Prestasi Tinggi (HPLC). Kemudian, kajian transformasi bersama kristal diteruskan dengan mengubah nisbah asid fumaric dan carbamazepine menggunakan kaedah buburan. Carbamazepine dan asid fumaric dicirikan menggunakan Analisis Gravimetrik Terma (TGA) dan Spektroskopi Inframerah Transformasi Fourier (FTIR). Hasilnya menunjukkan keterlarutan carbamazepine dan asid fumaric meningkat apabila suhu meningkat. Spektroskopi Inframerah Transformasi Fourier (FTIR) menunjukkan spektrum frekuensi utama (penyerapan rantau dalam cm $^{-1}$) carbamazepine dan asid fumaric. Termo Gravimetrik Analisis (TGA) analisis menunjukkan jumlah penguraian carbamazepine kira-kira pada 250 ° C dan untuk asid fumaric pada 260 ° C. Sebagai kesimpulannya, kebolehlarutan carbamazepine dan asid fumaric telah meningkat apabila suhu meningkat. Disebabkan kekangan masa dan kegagalan teknikal bagi peralatan seperti (Kromatografi Cecair Prestasi Tinggi (HPLC)) semasa analisis telah menyebabkan kajian transformasi bersama kristal tidak dapat disiapkan.

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K_y	Transfer coefficient
rpm	Rotation per minutes

CHAPTER 1

INTRODUCTION

1.1 Background

Crystallization is the one part of chemical discipline that play an important criteria in chemical industries such as food industries, pharmaceutical field, chemical industries and many more. Crystallization is a separation and purification technique employed to produce a wide variety of materials. For an example, the separation process of salt from the sea water (Geankoplis, 2003).

Co-crystal can be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces. In the other definition of co-crystal is a crystalline structure made up of two or more components in a definite stoichiometric ratio, where each component is defined as either as atom, ion, or molecule (Morissette, 2004).

Co-crystal can be prepared by using several methods such as slow solvent evaporation, crystallization from solution, solvent-reduced (e.g. slurrying, solvent-drop grinding) and solvent-free [e.g. grinding, melt [(hot stage microscopy)], high throughput crystallization and co-sublimation techniques (Morissette, 2004). Co-crystals are usually prepared by slow solvent evaporation if only viable compatible solubility in a given solvent exists between the components comprising the potential co-crystal (Morissette, 2004).

Poor dissolution rate, solubility, chemical stability and moisture uptake influence the therapeutic efficacy of many pharmaceuticals, and significantly lower the market value of a drug. Multi-component crystals e.g. solvates, hydrates, co-crystals, salts play important role in the design of new solids particularly in the pharmaceutical area. For an example carbamazepine is an active pharmaceutical ingredients (API) that usually used in pharmaceutical industry typically for the treatment of seizure disorders and neuropathic pain. It may be used as a second line treatment for bipolar disorder and along with anti psychotic agents in schizophrenia. In this case the carbamazepine alone is stable but we did know the stability and the solubility of the carmabazepine when it added with other component such as fumaric acid that can possibly give the lime taste in the carbamazepine when taken as a tablet. By adding the co former that can form a co-crystal, we can increase the market value of the carbamazepine (Yadav et al., 2009).

The key benefits associated with co-crystallization approach to modify properties of pharmaceutical solids are the theoretical capability of all types of drug molecules, including weakly ionizable and non-ionizable to form co-crystals, and the existence of numerous, potential counter-molecules, including food additives, preservatives, pharmaceutical excipients as well as other APIs, for co-crystal synthesis. Major advantage that co-crystal synthesis may offer to the pharmaceutical industry is an opportunity to address intellectual property (IP) issues by extending the life cycles of old APIs (Yadav et al., 2009).

It is important to know that salt formation is generally directed at a single acidic and basic functional group. But co-crystals can simultaneously address multiple functional groups in a single drug molecule. In addition space is not limited to binary combinations (acid-base pairs) since tertiary and quaternary co-crystals are realistic one (Andrew, 2006). Co-crystal was observed that to provide a powerful means to tailor the desired solubility and dissolution-pH dependence of APIs, even when the API is a non-ionizable molecule (Koji et al., 2006).

1.2 Objective of Study

The objective of study is to study solid phase transformation and stability of carbamazepine-fumaric acid co-crystal.

1.3 Scope of Study

The first scope of study is to measure the solubility of fumaric acid, carbamazepine and carbamazepine-fumaric acid co-crystal. The solubility measurement can be measure using gravimetric and High Performance Liquid Chromatography (HPLC) method. The second scope is to characterize the fumaric acid and carbamazepine using Thermal Gravimetric Analysis (TGA) and Fourier Transform Infrared Spectroscopy (FTIR). And the final scope is to analyze the process transformation ofthe carbamazepine-fumaric acid co-crystal with different mole ratio of fumaric acid over carbamazepine.

1.4 Problem Statements

The high market value for a particular drug (carbamazepine) in pharmaceuticals with low solubility is the biggest challenge in the field of pharmacy where the solubility is very important to improve the quality of any type of medication.

1.5 Significant of the Research

The developments of method in determine the solubility of the drug is very important in pharmaceutical area because the analysis is importance in routine quality control analysis (HPLC). The knowledge about the analytical equipments is important to ensure the measurement result is accurate. Extracted and analyze the result from the analytical equipment and method are important to analyze the unknown component.

1.6 Report Layout

This report is divided into five topics where it starts with an introduction and ends with the conclusion and future suggestion. The layout of the report is as follows:

- Chapter one briefly introduce the introduction of this study where it contain the background, objective of study, scope of study, problem statements and significant of research.
- Chapter two discuss about literature review which contain the fundamentals of crystallization and co-crystal, development and methods of crystallization and co-crystal, co-crystal characterization, and high performance liquid chromatography (HPLC).
- Chapter three clarifies the research materials and explains the research methodology of this study.
- Chapter four explains the result and discusses the result.
- Chapter five contain conclusion and recommendations

CHAPTER 2

LITERATURE REVIEW

2.1 Fundamentals of Crystallization and Co-Crystal

2.1.1 Crystallization

A crystal can be defined as solid composed of atoms, ions, or molecules which are arranged in an orderly and repetitive manner. The atoms, ions or molecules are located in three dimension arrays or space lattices (Geankoplis, 2003). Each lattice site has the same environment in the same direction. The structure associated with the lattice can be carved up into boxes (unit cells) that pack together to reproduce the whole crystal structure (Geankoplis, 2003).

Crystallization is the process where the solid particles are formed a homogeneous phase. We can see the process where water freezing to form ice or in nature we can observe the formation of snow from a vapor. The process has also included the formation of solid particle from a liquid melt. By the way the most important process is formed of solid crystal from a liquid solution where this process is used widely in industries. In crystallization the solution is concentrated and usually cooled until the solute concentration become rater that it solubility at a certain temperature and then the solute comes out of the solution and forming crystals approximately pure solute (Geankoplis, 2003). In industrial crystallization, the two phase mixture mother liquor and crystals of all size, which occupy the crystallizer and are withdrawn as a product called magma (MaCabe et al., 2005).

As we know, well formed crystal itself is nearly pure, but it retain other liquor when removed from the final magma, and if the crop contains crystalline aggregate, a considerable amount of mother liquor may be occluded within the solid mass (MaCabe et al., 2005). When retained mother liquor of low purity is dried on the product, contamination result, the extent of which depend on the amount and degree of impurities of the mother liquor retained by the crystal. In practice, much of the retained mother liquor is separated from the crystal by filtration or centrifuging, and balance is removed by washing with the fresh solvent. The effectiveness of these purification steps depends on the size and uniformity of the crystal (MaCabe et al., 2005).

The most important objective in crystallization is good yield and high purity but the appearance and size range of crystalline product are also important. If the crystals are to be further processed, reasonable size and size uniformity are desirable for filtering, washing, reacting with other chemical, transporting and storing the crystals (MaCabe et al., 2005).

Since all crystal of a definite substance has the same interface angle in spite of wide differences in the extent of development of individual faces, crystal forms are classified on the basis of this angle. There are seven classes of crystals, depending upon the arrangement of the axes to which the angle is referred that are cubic system, hexagonal, trigonal, tetragonal, orthorhombic, monoclinic and triclinic (MaCabe et al., 2005).

The relative development of different types of face of a crystal may differ depending on the solute crystallizing. For the example of sodium chloride crystallized from aqueous solution with cubic faces only. But if sodium chloride crystallizes from an aqueous solution with a given slight impurity present, the crystal will have octahedral faces. Both types are crystal; however they are in the cubic system. The crystallization in overall shape of the plates or needles has no relation to the type of crystal system and usually depends upon the process condition under which the crystal are grown (Geankoplis, 2003).

2.1.2 Co-Crystal

Co-crystal is a crystal-engineering technique employed in case of non-ionizable organic molecules that are unable to form salts. The aim of such a process is to obtain a new solid form with acceptable bio-pharmaceutical properties (Serajuddin, 2007).

There are many definitions in term of co-crystal. Co-crystal original defined as the adduct between two neutral solids at ambient conditions held together by hydrogen bonds in the crystalline material. Co-crystal also may be defined as a crystalline material that consists of two or more molecules (and electrically neutral) species held together by non-covalent forces. In the other definition of co-crystal is a crystalline structure made up of two or more components in a definite stoichiometric ratio, where each component is defined as either as atom, ion, or molecule. We also can state that a co-crystal is a crystalline structure composed of at least two components, where the components may be atoms, ions or molecules. A more inclusive definition is that co-crystals 'consist of two or more components that form a unique crystalline structure having unique properties' (Aakeröy, 2007).

Co-crystal and salts may sometimes be confused. The understanding of the fundamental difference between a salt formation and a co-crystal is very important to both pre-formulation activities and chemical/pharmaceutical development aspects. Indeed, salts and co-crystals can be considered as opposite ends of multi-component structures (Aakeröy, 2007). Salt are often chosen instead of the free acid or base as these can improve crystalline, solubility and stability of a pharmaceutical compound. Co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionizable sites in the API (Aakeröy, 2007).

2.2 Development and Methods of Crystallization

2.2.1 Crystal Growth

Crystal growth is a diffusion process, modified by the effect of the solid surfaces on which the growth occurs. Solute molecules or ions reach the growing faces of a crystal by diffusion trough the liquid phase. The usual mass transfer coefficient k_y applied to this step. On reaching the surface, the molecules or ions must be accepted by the crystal and organized into the space lattice. The reaction occurs at the surface at a finite rate, and the overall process consists of two steps in the series. Either the delusional or the interface steps will proceed unless the solution is supersaturated (MaCabe et al., 2005).

2.2.2 Nucleation

The rate of nucleation is the number of new particles formed per unit time per unit volume of magma or solid free mother liquor. This quantity is the first kinetic parameter controlling the crystal size distribution (CSD) (MaCabe et al., 2005).

2.2.2.1 Primary Nucleation

In scientific usage, nucleation refers to the birth of every small body of a new phase within a supersaturated homogenous existing phase. Basically, the phenomenon of nucleation is the same for crystallization from solution, crystallization from melt, condensation of fog drops in a super cooled vapor, and generation of bubbles in a super heated liquid. In all instances, nucleation is a consequence of rapid fluctuation on a molecular scale in a homogenous phase that is in a state of metastable equilibrium. The basic phenomenon is called homogenous nucleation, which is further restricted to the formation of new particles within a phase uninfluenced in any way by solid of any short, including the walls of the contain error even the most minute particles of foreign substances (MaCabe et al., 2005).

Another type of nucleation occurs when solid particles of foreign substances do influence the nucleation process by catalyzing an increase of nucleation rate at a given super saturated or giving a finite rate at a supersaturation where homogenous nucleation would occur only after a vast time. This is called heterogeneous nucleation (MaCabe et al., 2005).

2.2.2.2 Secondary Nucleation

The formation of nuclei attributable to the influence of the existing macroscopic crystal in the magma is called secondary nucleation (MaCabe et al., 2005).Two kinds are known, one attributable to fluid share and the other to collisions between existing crystal with one another or with the wall of the crystallizer and rotary impeller or agitator blades (MaCabe et al., 2005).

2.2.3 Equipment in Crystallization

Commercial crystallizer may operate either continuous or batch wise but for special applications, continuous operation is preferred. The first requirement of any crystallizer is to create a supersaturated saturation solution, because crystallization cannot occur without supersaturation (MaCabe et al., 2005). Crystallizing equipment can be classified according to the methods uses to bring about the supersaturated as follows:

I) Supersaturation produced by cooling the solution with negligible evaporation-tank and batch type crystallizer(Geankoplis,2003).

II) Supersaturation produced by evaporation of the solvent with a little or no cooling-evaporator-crysatallizer and crystallizing evaporators (Geankoplis, 2003).

III) Supersaturation by combining cooling and evaporation in an adiabatic evaporator-vacuum crystallizer (Geankoplis, 2003).

In crystallizers producing supersaturation by cooling, the substances must have a solubility curve that decreases markedly with temperature. This occurs for many substances, and this method is commonly used. When the solubility curve changes little with temperature, as for common salt, evaporation of the solvent to produce supersaturation is often used. Sometimes evaporation with some cooling may use. In the method of cooling adiabatically in vacuum, a hot solution is introduced into a vacuum, where the flashes or evaporates and the solution is cooled adiabatically. This method for producing supersaturation is the important for large scale production liquid (Geankoplis, 2003).

2.2.4 Variant in Crystallizers

Commercial crystallizer may also be differentiated in several other ways. One important differences in how the crystals are brought into contact with the supersaturated liquid (MaCabe et al., 2005).

The first technique calls the circulating-liquid method where a stream of supersaturated solution is passed through a fluidized bed of growing crystals, within which supersaturation is released by nucleation and growth. The saturated then is pumped through a cooling or evaporated zone, in which supersaturation is generated and finally the supersaturated solution is recycled through the crystallization zone (MaCabe et al., 2005).

In the second technique called circulating-magma method, where the entire magma is circulated through both crystallization and supersaturation steps without separating the liquid from the solid. Supersaturation as well as crystallization occurs in the percentage of crystals. In both methods feed solution is added to the circulating stream between the crystallizing and supersaturated zone (MaCabe et al., 2005).

One type of crystallizer uses size classification devices designed to retain small crystal in the growth zone for the further growth and allow only crystals of a specified minimum size to leave the unit as the product. Ideally, such a crystallizer would produce a classified product of a single uniform size. Other crystallizer is designed to maintain a thoroughly mixed suspension in the crystallizing zone, in which crystal of all size from nuclei to large crystals are uniformly distributed throughout the magma. Ideally, the size distribution in the product from a mixer suspension unit is identical to that in the crystallizing magma itself (MaCabe et.al, 2005).

To make the average crystal size larger than that for a mixed-suspension unit, some crystallizers are equipped with a device that segregate and remove most of the fine crystal from the crystallizing zone. These small crystals are dissolved again and return to the crystallizer. Other crystallizer has two take off lines, one for large crystal and one for the other one. The two product streams, which may differ considerably in volume, are combined and send to a filter or separation unit. This technique is for enhancing the crystal (MaCabe et al., 2005).

Most crystallizers utilize some form of agitation to improve growth rate, to prevent segregation of supersaturated solution that causes excessive nucleation and to keep crystal in suspension throughout the crystallizing zone. Internal propeller agitator may be used, often equipped with draft tube and baffles, and external pump also are common for circulating liquid or magma through the supersaturating or crystallizing zone. This method called force circulation. One advantage of force circulation unit with heater is that several identical unit can be connected in multiple effects by using the vapor from one unit to heat the next in line. This system is called evaporator crystallizers (MaCabe et al., 2005).

2.3 Development and Methods of Co-Crystal

This chapter is discussed about the method and development of the co-crystal. There are two methods in development of co-crystal in term to increase the rate of co-crystal formation. The first method is based on solution and the second method is a dry method (Jones et al., 2005).

2.3.1 Co-Crystal Slow Evaporation

A Co-crystal that formed from the slow evaporation method is only viable if compatible solubility in a given solvent exists between the components comprising the potential co-crystal. (Alexenderet al., http://ebookbrowse.com)

An experiment was conducted by Basavoju et al (2008) where there are combine a 1:1 mixture of indomethacin (35.78 mg, 0.1 mmol) and saccharin (18.32 mg, 0.1 mmol) slow evaporation method. In this method the indomethacin and saccharin is added with ethyl acetate in a 25 ml conical flask and heated to aid dissolution. Then the solution was allowed to evaporate slowly in a controlled fume hood (temperature 22-C, air flow 0.54 m/s) to produce co-crystals (Basavoju et al., 2008)

As the result, the co-crystal has been observed by using an optical micro graph to analyze the shape of the co-crystal (Basavoju et al., 2008). The Figure 2.1 shows the optical micrograph of IND–SAC co-crystal.

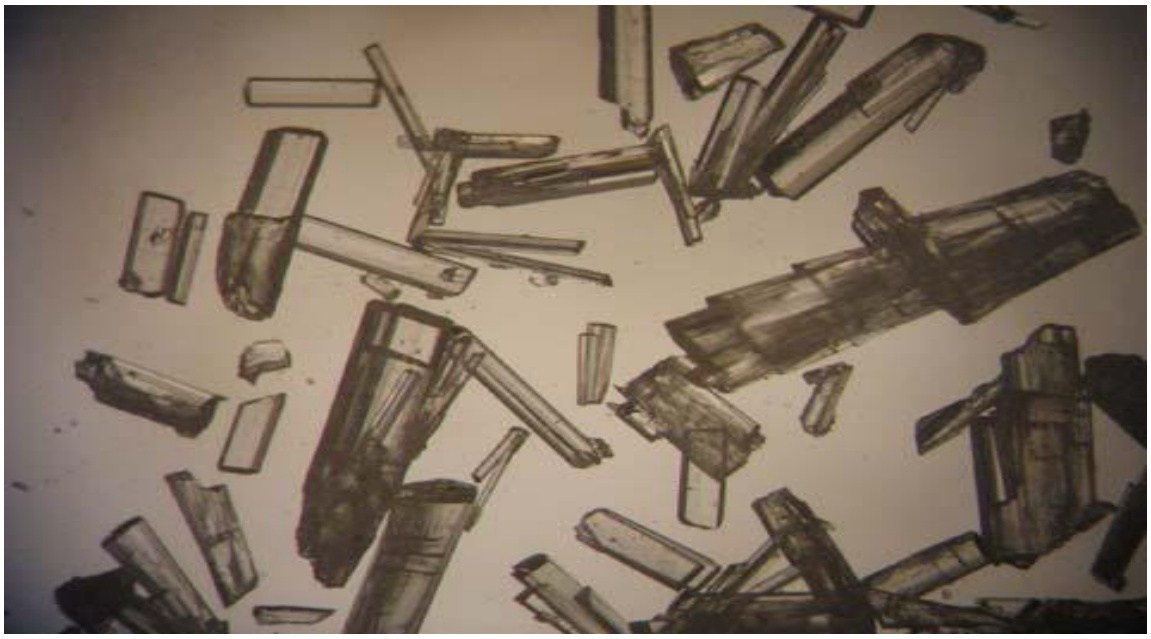

Figure 2.1: Optical micrograph of IND–SAC co-crystal.

Source: Basavoju et al., 2008

2.3.2 Grinding Process

Grinding has attracted interest in the formation of co-crystals. Both dry grinding and liquid-assisted grinding are techniques employed in order to produce these materials (Jones et al., 2005).

In dry grinding, co-crystal formers are ground together manually using a mortar and pestle. Dry grinding process can also be conducted using the machine as using a ball mill, or using a vibratory mill (Jones et al., 2005). Figure 2.2 shows the example of ball mill 8000 mixer laboratory scale.